Aluminum-Catalyzed Hydroboration of Alkenes

Aluminum-catalyzed hydroboration of alkenes

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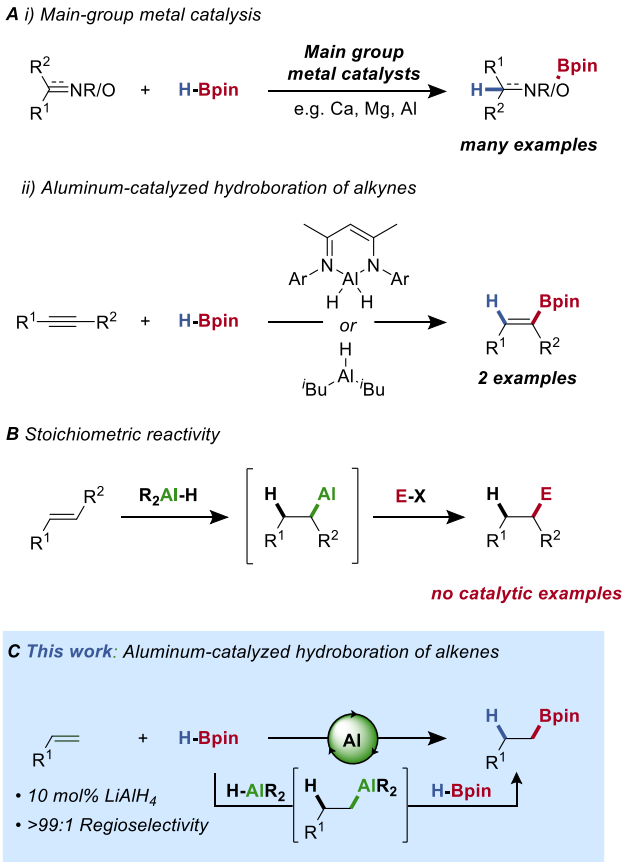
ABSTRACT: The aluminum-catalyzed hydroboration of alkenes with HBpin is reported using simple commercially available aluminum hydride precatalysts [$LiAlH_4$ or sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al)]. Good substrate scope and functional group tolerance is demonstrated for alkene hydroboration, and the protocol was also applied to the hydroboration of ketone, ester and nitrile functional groups, showing the potential for wider application. The aluminum-catalyzed hydroboration is proposed to proceed by alkene hydroalumination which generates an alkyl aluminum species that undergoes σ-bond metathesis with HBpin to drive turnover of the catalytic cycle.

KEYWORDS hydroboration, alkene, aluminum, main group, catalysis.

The increasing need for sustainable chemical processes has cemented catalysis at the core of modern industrial chemistry and academic research. Industrial catalysis is dominated by heavy, precious transition metals[1], thus considerable efforts have been invested in Earth-abundant metal[2] and main-group metal[3] alternatives. Main-group metals offer a powerful and sustainable alternative to transition metal species, but the lack of available d-orbitals renders traditional catalytic cycles challenging. Almost exclusively, main-group metal catalysis has been limited to more reactive, polar substrates with s- and p-block metal complexes developed for the catalytic reduction of unsaturated polar bonds (C=O, C=NR, *etc.*) (Scheme 1, **A** *i*).[4–7] Of the main-group (*psuedo*)metals, aluminum offers the greatest abundance, however catalytic reductions using aluminum species have been limited to carbonyl reduction and alkene polymerization.[8] To the best of our knowledge, only 2 aluminum species have been reported for the catalytic reduction of carbon-carbon multiple bonds and these are limited to alkyne hydroboration (Scheme 1, **A** *ii*).[9] Although stoichiometric alkene reduction has been reported (Scheme 1, **B**), the catalytic reduction of alkenes using an aluminum species has yet to be realized. To offer complimentary reactivity to transition metal catalysts[10] a general aluminum-catalyzed protocol for the hydroboration of unsaturated bonds is needed.

Organoboron species are key building blocks[11-15] in organic synthesis and thus, uniquely the perfect target for the development of sustainable synthetic methods. We have previously used alkyne hydroalumination as a route to alkenyl boronic esters.[9b] However, the analogous reaction with alkenes is far more challenging[16] and was unsuccessful under these conditions. We postulated that with correct aluminum design, reduced steric bulk and increased Lewis basicity, alkene hydroalumination could potentially be used as a first-step in a catalytic hydroboration of alkenes. Ideally, the aluminum catalyst would be commercially available and easily handled. Alane is the simplest aluminum hydride, has minimal steric bulk and high Lewis basicity, thus we began by screening alane as a hydroboration catalyst.

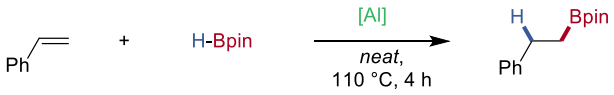


Scheme 1. A) Established reactivity. B) Stoichiometric reactivity. C) This work: aluminum-catalyzed hydroboration of alkenes.

Using $H_3Al{\cdot}NMe_3$ (5 mol%) and pinacol borane, HBpin, (1.2 eq.) the hydroboration of styrene proceeded in 83% yield to give the anti-Markovnikov (linear) alkyl boronic ester within 4 hours (Table 1, Entry 1). As alane is not commercially available and requires the strictest of inert environments, we next trialled more stable and easily handled aluminum reagents. Both $Et_3Al{\cdot}DABCO$ and commercially available $^{i}Bu_2AlH$ (DIBAL-H) gave the linear boronic ester, albeit in decreased

yield (40% and 55% respectively, Entries 2 and 3). In order to increase the reactivity of the aluminum reagent we moved to the more hydridic bis(2-methoxyethoxy)aluminum hydride (RED-Al) which gave the linear boronic ester in excellent yield and regioselectivity (Entries 4 and 6). As a tetracoordinate aluminum hydride proved successful we also trailed $LiAlH_4$, the most readily handled and widely used aluminum hydride. Using $LiAlH_4$, the hydroboration of styrene was successfully catalysed and the linear boronic ester obtained in excellent yield, with a regioselectivity of 99:1 linear to branched products (Entries 5 and 7). Presumably, *in situ* conversion to the AlH_3 by reaction with HBpin, proceeds during catalysis. Inspired by the recent reports of nucleophile-initiated hydroboration reactions[17, 18] we decided to investigate other metal hydrides under our reaction conditions. Although both LiH and NaH were active catalysts, the decreased yields using these hydride reagents suggests a catalytic role for aluminum beyond simple hydride delivery. Although unlikely when alkyl alanes are used (entries 2 and 3, see later), we cannot exclude a catalytic role for a borane species obtained by hydride-mediated decomposition of HBpin when hydride salts are used as the catalyst.[18]

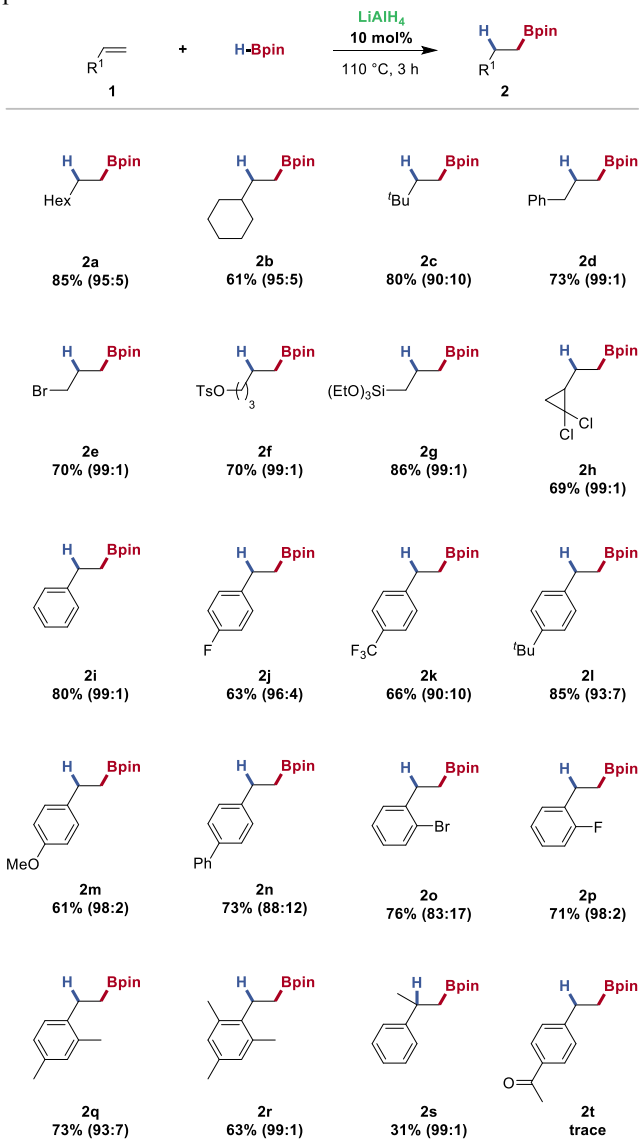
Table 1. Optimization of Reaction Conditions[a]



Entry	Catalyst	Yield (%)
1	AlH_3•NMe_3 (5 mol%)	83
2	Et_3Al•DABCO (5 mol%)	40
3	$^{i}Bu_2Al$-H (5 mol%)	55
4	Red-Al (5 mol%)	85
5	**$LiAlH_4$ (5 mol%)**	**86**
6	Red-Al (10 mol%)	95
7	**$LiAlH_4$ (10 mol%)**	**95**
8	LiH (10 mol%)	43
9	NaH (10 mol%)	48

[a]Reaction conditions: catalyst (5-10 mol %), styrene (0.45 mmol) and HBpin (0.54 mmol, 1.2 eq.), *neat*, heated to 110 °C for 4 h. Yields determined by ^{1}H NMR from the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

Screening of the reaction parameters (solvent, temperature, etc.) led to optimized conditions of $LiAlH_4$ or Red-Al (10 mol%), alkene (1 equiv.) and HBpin (1.1 equiv.) at 110 °C for 3 hours. With these conditions, we explored the substrate scope and functional group tolerance of this hydroboration protocol (Scheme 2). Terminal alkyl-substituted alkenes all underwent successful hydroboration to the linear alkyl boronic ester with excellent control of regioselectivity (Scheme 2, **2a-2h**). Very little variation in catalyst activity was observed across alkenes bearing primary, secondary and tertiary alkyl substituents (**2a-c**). Halide- (**2e**), silyl- (**2f**) and tosyl-substituents (**2g**) were all tolerated without catalyst inhibition or alkene reduction to the alkane[19] showing the potential for further product functionalization. The successful hydroboration of 1,1-dichloro-2-vinylcyclopropane (**2h**) proceeded without cleavage of the C-Cl bonds or cyclopropane ring-opening.[20] Styrene derivatives bearing both electron-withdrawing and electron-donating functionalities (**2j-2p**) all gave good yields and regioselectivities demonstrating a negligible electronic effect. Increasing the steric demands of the styrene derivatives (**2q-2s**) also showed a negligible effect on hydroboration yield and regioselectivity, even in the case of 2,4,6-trimethyl styrene (**2r**). The selective hydroboration of alkene functionality in the presence of a ketone was not possible, with hydroboration leading to a complex mixture of products with no evidence of chemoselective hydroboration at either functionality (**2t**). A list of unsuccessful substrates is reported in the SI.

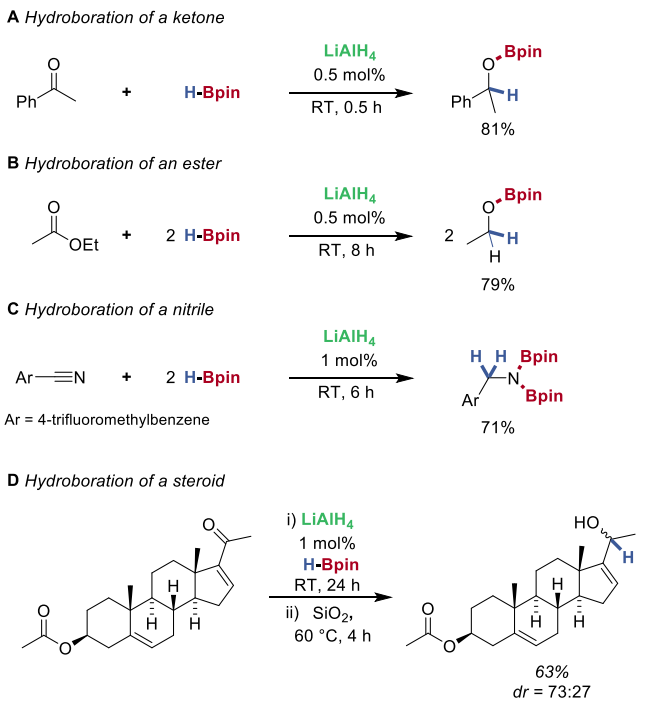


Scheme 2. Substrate Scope. Isolated yield using $LiAlH_4$ (10 mol%), neat, 3 h, 110 °C; ratios in parentheses report the distribution of regioisomers (linear/branched).

To further demonstrate the applicability of this protocol we applied our aluminum-catalyzed hydroboration to polar functionalities. Here, the rate of hydroboration would need to significantly outcompete the background rate of the direct addi-

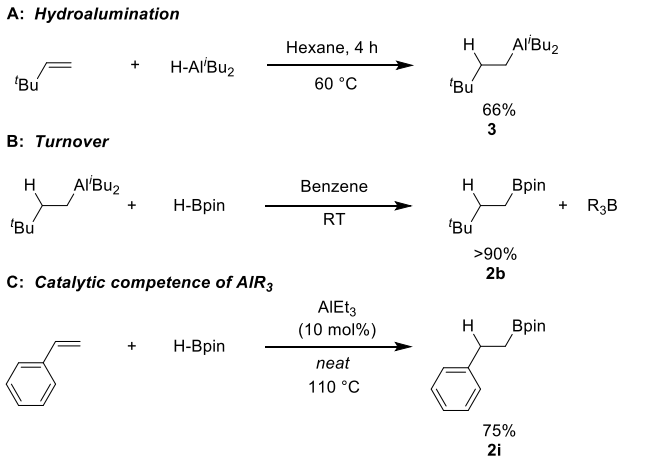
tion of $LiAlH_4$ to the polar bond. Hydroboration of acetophenone was successfully promoted by just 0.5 mol% of $LiAlH_4$ at room temperature in only 30 minutes, with an 81% isolated yield (Scheme 3, A). This catalytic activity is, to the best of our knowledge, the highest for aluminum-catalyzed hydroboration of ketones[8b,c] with a TON of 162 and additionally demonstrates a new level of operational simplicity. With hydroboration of a ketone demonstrated, we wondered if the same protocol could be applied to the more challenging ester hydroboration. Again, using 0.5 mol% of $LiAlH_4$, ethyl acetate was successfully hydroborated to the boronic ester in 79% yield in 8 hours at room temperature (Scheme 3, B).[21]

With success in ketone and ester hydroboration, we next trialed the hydroboration of a nitrile. Here a stronger triple bond would need to be reduced and the intermediate aluminum-nitrogen bond turned over. Using 4-trifluoromethylbenzonitrile as a model substrate, $LiAlH_4$ (1 mol%) catalyzed the hydroboration of the nitrile in 6 hours at room temperature to give the amido boronic ester in 71% isolated yield (Scheme 3, C); showing catalyst activity comparable to transition metals,[22] and exceeding the single example for main group species previously reported.[4c,23] Hence we believe that this protocol has potential for further reductive transformations of polar compounds. This protocol was also applied to the hydroboration of a steroid, 16-dehydropregnenolone acetate bearing alkene, ester and ketone functionalities (Scheme 3, D). In contrast to the reaction with stoichiometric $LiAlH_4$[24] the hydroboration was chemoselective for the ketone to give the secondary alcohol, after SiO_2-mediated hydrolysis, in 63% isolated yield.



Scheme 3. Aluminum-catalyzed hydroboration of polar bonds. A) Hydroboration of acetophenone. B) Hydroboration of ethyl acetate. C) Hydroboration of 4-trifluoromethylbenzonitrile. D) Hydroboration of 16-dihydropregnenolone acetate.

Based on the precedent established for the aluminum-catalyzed hydroboration of the alkynes[8b] we hypothesized that this reaction may occur following a similar mechanism; alane generation, hydroalumination and σ-bond metathesis between the alkyl-aluminum and H-Bpin to form the boronic ester and regenerate the alane catalyst. Stoichiometric reaction of Red-Al or $LiAlH_4$ with different aryl- and alkyl-alkenes proved to be unsuccessful due to competing alkene polymerization. However, using $^{i}Bu_2Al$-H, stoichiometric reaction with 3,3-dimethyl butene gave the corresponding alkyl aluminum species **3** in 66% isolated yield within 4 hours at 60 °C (Scheme 4, A). Treatment of the isolated alkyl aluminum species **3** with HBpin immediately gave the alkyl boronic ester **2b** (Scheme 4, B), with concurrent formation of trialkyl borane species. Although, under these conditions, the exchange behavior of alanes AlX_3 and boranes BY_3 generates mixtures of the 'scrambled' alanes and boranes (e.g. AlX_nY_{3-n}, BY_nX_{3-n}),[25-26] this suggests that the crucial C-B bond-forming step occurs with concomitant Al-H regeneration.[17a] The catalytic activity of the trialkyl aluminum intermediate was confirmed using $AlEt_3$ (10 mol%), as a surrogate of alane **3**, under our optimised conditions to give the boronic ester in 75% yield (Scheme 4, C). Based on these experiments, we propose a catalytic cycle whereby the alkene undergoes hydroalumination followed by a σ-bond metathesis of the resulting alkyl aluminum species with pinacol borane (aluminum-boron exchange). This step releases the alkyl boronic ester product and regenerates the alane catalyst.



Scheme 4. Mechanistic investgations. A) Hydroalumination of 3,3-dimethyl butene. B) Turnover; Al-B exchange. C) Catalytic competence of a trialkyl aluminum species.

We have used hydroalumination and Al-B exchange reactions to provide a simple and economical synthesis of alkyl boronic esters using simple, commercially available aluminate salts as catalysts. Mechanistic studies are consistent with an aluminum-hydride-catalyzed hydroboration proceeding by initial hydroalumination, followed by σ-bond metathesis to exchange aluminum and boron, and regenerate the aluminum hydride. However, we cannot rule out a mechanism involving a borohydride or borane species as part of the catalysis.[27] Our hydroboration protocol was also successful for the hydroboration of polar bonds including ketone, ester and nitrile functionalities, and for the first time showing unprecedented activity in main group-catalysis and comparable to transition metal catalysts. We are currently working to expand the scope of this method in terms of both the electrophile and substrate.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compounds characterization

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Notes

The Authors declare no competing financial interest.

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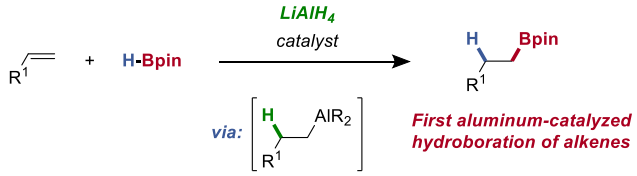

First aluminum-catalyzed hydroboration of alkenes

General hydroboration method

- *Single protocol*
- *Simple & commercially available catalyst*